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Brainstem Tumours in Children: Consecutive Case Series of 42 Patients

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Summary

Objective: To study the pre-diagnostic symptomatic interval, the signs and symptoms at diagnosis and the long-term outcome of paediatric brainstem tumours.

Methods: We reviewed 42 consecutive patients under 16 years of age (median age at diagnosis 5.5 years) who were diagnosed between January 1980 and December 2010 at the University Children's Hospital of Zurich, Switzerland.

Results: The most frequent symptoms and signs at diagnosis were: cranial nerve palsies (61%), usually affecting eye movement, increased intracranial pressure (61%) and abnormal gait and coordination (59%). In children younger than 4 years (29%): most common initial signs were abnormal gait and coordination (58%) and head tilt (58%). 93% of the patients presented with three or more symptoms/signs at diagnosis. The median pre-diagnostic symptomatic interval was 48 days (range 0 to 395 days) with a median parents' delay of 19 days and a median doctor's delay of 7 days. Treatments included surgery (19/42 [45%]), radiotherapy (15/42 [36%]) and chemotherapy (12/42 [29%]). Median progression-free survival was 5.7 months and median overall survival was 16.6 months. Median overall survival was 7.9 months in patients with tumour localization in the pons compared to the others with a median survival of 36.3 months. Median progression-free survival of 4.8 months and a median overall survival of 9.6 months were seen in children with diffuse intrinsic brainstem gliomas. Treatment of these patients with surgery, radiotherapy, chemotherapy or a combination resulted in a significant better median progression-free (p=0.042) and median overall survival (p=0.001) than observational treatment.

Conclusion: Children with brainstem tumours present with various often unspecific signs and symptoms. The combination of multiple neurological signs and symptoms should alert the clinician and lead to CNS imaging without delay. The prognosis of diffuse intrinsic pontine tumours is dismal.

1. Introduction

In children, tumours of the central nervous system (CNS) are the most common group of solid tumours and the second most common malignancy, after leukaemia. This is equally true for the U.S. [1], for Europe [2] as well as for Switzerland [3]. CNS tumours account for up to 30 % of all tumour types in children [4]. Among paediatric CNS tumours, tumours within the brainstem constitute 10-15 % [5, 6]. No gender predominance could be found [5, 7-13]. Brainstem tumours occur primarily in children and arise rather seldom in adults [6, 7, 14-16]. Prognosis and treatment of these tumours depend mainly upon location within the brainstem.

1.1 Classification of brainstem tumours

Brainstem tumours are a heterogeneous group of tumours that have markedly differences in biologic behaviours and prognoses. The majority of them are gliomas [17]. Standard method for diagnosis of brainstem tumours is magnetic resonance imaging because the eloquent location of these lesions makes biopsy difficult [18, 19]. Computed tomography is not the imaging modality of choice, because many of these tumours are isointense [20-22]. Neuroimaging characteristics divide these tumours into two groups: diffuse intrinsic tumours and focal tumours [23, 24]. Diffuse intrinsic brainstem glioma account for 80 % of paediatric cases. They have a dismal prognosis [25]. Most of them are high-grade, locally infiltrative tumours, either anaplastic astrocytomas (WHO-grade III) or glioblastomas (WHO-grade IV) [26]. Focal brainstem tumours constitute the other 20 % of the cases [26]. They include midbrain tumours, dorsal exophytic brainstem tumours, and cervicomedullary junction tumours [6, 23]. Histopathologically, most of these tumours are low-grade astrocytomas, usually pilocytic astrocytomas (WHO-grade I) [18]. Tumours without pontine involvement are described to be almost low-grade, showing a more favourable outcome [5].

1.2 Diffuse intrinsic brainstem gliomas

Due to their unresectable nature, devastating neurological lesions and poor response to adjuvant therapy, diffuse tumours infiltrating the brainstem have the worst prognosis of all brain tumours in children [25]. They usually present with a brief symptomatic period and evident neurological involvement. Magnetic resonance imaging alone is usually sufficient for diagnosis of diffuse intrinsic brainstem glioma, and it obviates the need for a surgical biopsy for diagnosis in most cases [27-29]. Characteristics on magnetic resonance imaging are a typically poorly margined, hyopintense lesion on T1 and hyperintense lesion on T2 weighted images, with variable contrast enhancement. Because of the associated morbidity with surgery in this eloquent region of the brain, biopsies should be reserved for patients with atypical imaging findings, in order to identify patients with tumours not being high-grade lesions [29-31]. Due to the development of targeted therapies, the issues of stereotactic or open biopsies for diffuse

brainstem gliomas are currently being readdressed [28, 32]. Palliative corticosteroid therapy is common practice in children with symptomatic tumours [25]. Symptoms of peritumoural edema can rapidly improve after the administration of corticosteroids. Standard treatment consists of conventional fractionated local radiotherapy, which can lead to transient neurological improvement with a progression-free survival benefit, however, radiotherapy does not result in an increase of the probability for cure [6, 27, 28]. In order to reduce patients' treatment burden, hypofractionated radiotherapy has been used as an alternative with a shorter treatment time [28, 33-35]. No alternative radiation therapy technique has improved the survival outcome of children with diffuse intrinsic tumours [35-41]. So far, the application of chemotherapeutics either before, during or after radiation therapy has not resulted in a survival advantage in children with diffuse intrinsic brainstem gliomas [11, 42-49]. Most studies reveal a median overall survival time of shorter than one year, and nearly all children eventually die [6, 28, 50].

1.3 Focal brainstem tumours

These tumours are subclassified according to their anatomic location: midbrain focal tumours, dorsal exophytic tumours and cervicomedullary junction tumours. Focal tumours are typically well circumscribed on magnetic resonance imaging, without local invasive growth or edema, but may be compressive or cystic. Characteristics on magnetic resonance imaging are a typically hyopintense lesion on T1 weighted images and a hyperintense lesion on T2 weighted images with uniform contrast enhancement [19, 51]. Calcifications can be present in focal tumours of the midbrain with poor contrast enhancement [14]. Tectal gliomas typically exhibit a nonenhancing thickening of the tectal plate [19]. Hydrocephalus is often associated with tectal tumours and in dorsally exophytic brainstem tumours [6, 50, 52]. For cervicomedullary tumours, characteristic imaging findings are hypointense lesions on T1 weighted images and hyperintense lesions on T2 weighted images [20]. Differentiation of low-grade from high-grade brainstem gliomas is often possible by magnetic resonance imaging and biopsy is only indicated if diagnosis cannot be established due to atypical findings [51, 53, 54].

Focal brainstem tumours may be treated with surgery, radiation, chemotherapy or with conservative treatment. Hydrocephalus can be managed by cerebrospinal fluid diversion [55]. In contrast to diffuse tumours, surgical tumour debulking in dorsal exophytic tumours [56, 57] and cervicomedullary tumours [58, 59] is the preferred treatment. If surgical tumour resection is contraindicated, with stereotactic biopsy, important histological information can be obtained to guide further treatment [60]. In cases of tumour recurrence after resection, chemotherapy, radiotherapy or a second surgical tumour resection can be considered [61, 62]. Tectal tumours can cause aqueductal obstruction with increased intracranial pressure [18, 52, 63]. Initial therapy consists of cerebrospinal fluid diversion. Third ventriculostomy is described to be superior to a ventriculoperitoneal shunt, avoiding shunt malfunctions and the insertion of foreign

objects [52, 64, 65]. Conventional radiation therapy may be an option in patients with inoperable tumours, with residual disease after surgery or may be deferred until there is disease progression [54]. There is no additional survival benefit from hypofractionated (once per day) or hyperfractionated radiotherapy compared to conventional radiation therapy [66, 67]. Chemotherapy for children with unresectable or progressive low-grade tumours involving the brainstem is playing an increasing role. Chemotherapy has been described as a safe and effective treatment option for these children in order to delay and/or avoid radiotherapy [68, 69]. In summary, the subgroup of focal brainstem tumours, predominantly of low-grade histology, is associated with a favorable prognosis.

1.4 Brainstem gliomas associated with Neurofibromatosis type 1

Neurofibromatosis type 1 (NF 1) is a common genetic disorder, with an incidence of approximately 1 in 2600 to 1 in 3500 [70-72]. NF 1 predisposes patients to the development of both benign and malignant tumors from peripheral or central nerve tissue [73-75]. Most of the CNS tumours are pilocytic astrocytomas (WHO grade I) [76]. Prevalent CNS tumours in NF 1 are optic pathway, hypothalamic and brainstem gliomas [77-79]. These tumours behave in a much more benign fashion than their counterparts in non-NF 1 children [80]. Brainstem lesions in children with NF 1 behave in a biologically indolent nature and most do not require therapeutic interventions [79, 81-85].

1.5 Signs and symptoms

The symptoms and signs of brain tumours in children are by no means pathognomonic and often mimic other more common and less serious illnesses, making the diagnosis in the early stage often difficult [9, 86]. This fact is reflected in rather long pre-diagnostic symptomatic intervals (PSI) [86-91]. The expanded access to neuroimaging has resulted in a shorter interval between the first medical consultation and diagnosis (doctor's delay) [86]. Nevertheless, for patients with low-grade brainstem gliomas, relatively long histories of minor signs and symptoms are described [6, 14, 18, 20, 22, 26, 53, 56, 92].

Signs and symptoms of brainstem tumours depend on the location of the lesion and the age of the child. Patients with diffuse intrinsic brainstem gliomas can present with a rapid appearance of: long tract signs, ataxia and cranial nerve palsies most commonly affecting the sixth and seventh nerve. However, involvement of cranial nerves III, IV, IX and X may also be discovered, or personality changes noted as the first signs. Hydrocephalus is described as rare, except in tumours located in the tectal area or in dorsal exophytic tumours. These tumours often combine hydrocephalus with increased intracranial pressure [6, 50, 52, 63]. In diffuse intrinsic brainstem gliomas, an intratumoural hemorrhage can rarely be present [93]. Histories of nonspecific symptoms such as headache and vomiting can provoke a delay in the diagnosis of brainstem tumours.

The present study was undertaken to investigate delays in the diagnosis, the signs and symptoms at diagnosis and the long-term outcome of paediatric brainstem tumours.

2. Patients and methods

2.1 Patient selection and clinical data

42 patients, under the age of 16, with brainstem tumours were diagnosed at the University Children's Hospital of Zurich, Switzerland, between January 1980 and December 2010. Brainstem tumours were defined by the intra-axial location in the mesencephalon, pons or medulla oblongata. The following information was systematically derived from medical records of the 42 patients: date of birth, gender, age at diagnosis, pre-diagnostic symptomatic interval, the symptoms and signs at diagnosis, treatment modalities, progression-free survival, follow-up time and overall survival.

The pre-diagnostic symptomatic interval (PSI) was defined as the interval between the onset of symptoms/signs and the time of diagnosis by neuroimaging (magnetic resonance imaging (MRI) or computed tomography). In 29 out of 42 patients (69%), medical records allowed a subdivision of the PSI into an interval between sign/symptom onset and first medical consultation (parents' delay) and between the first medical consultation and diagnosis by neuroimaging (doctor's delay).

Last follow-up information was obtained in December 2010, and the data was validated and compiled for statistical analysis. Given the retrospective nature of the study, some of the data points were not available from medical records.

2.2 Pathology data

In case of tumour surgery or autopsy the histopathological diagnosis was recorded either out of patient's charts or pathology reports.

2.3 Imaging data

Regarding patients without histological diagnosis, presumptive diagnosis was based on radiological findings. Sources of detailed MRI tumour data were medical or radiological reports and re-analysis done together with a neuro-radiologist (Dr. med. Ianina Scheer) in 34 out of 42 cases. The tumour entity, based on neuroimaging, as well as the anatomical location and radiographic appearance observed in the MRI (when available) were recorded.

2.4 Treatment data

Treatments included surgical debulking, cerebrospinal fluid diversion, radiotherapy, chemotherapy and palliation.

2.5 Statistical analysis

Descriptive statistics were computed and survival curves with 95% confidence intervals (according to Peto) were calculated using the Kaplan Meier method with PASW Statistics 18 (Version 18.0.0) and R (Version 2.14.2). Survival time was measured from time of diagnosis to the date of last follow-up visit or death. Progression-free survival time was measured from diagnosis to obvious evidence of clinical and/or radiographic tumour progression.

Gender, age at diagnosis (age <4 and >4 years), radiologic appearance and tumour grade (high- versus low-grade), tumour localization and treatment modalities were evaluated by the Log Rank test (Mantel-Cox) and Breslow test (Generalized Wilcoxon) for their impact on survival. Median survival together with the corresponding 95% confidence interval (95% CI) was computed for each group. Results of the statistical analysis with p-value smaller than 0.05, were considered to be statistically significant. Whereas p-values larger than 0.05 and smaller than 0.1 were interpreted as tendency.

2.6 Ethical approval

The retrospective data collection for this study was approved by the Institutional Review Board Zurich (KEK 2011-0069/3).

3. Results

3.1 Patient and tumour characteristics

42 children were diagnosed with intra-axial tumours located within the brainstem, between January 1980 and December 2010. The median age at diagnosis was 5.5 years (0.0 - 14.6 years). 20/42 (48%) children were female and 22/42 (52%) male. 2/42 (5%) children showed an underlying cancer predisposition (NF 1).

Diagnoses were established by typical imaging in 34/42 (83%) and confirmed by histology in 23/42 (55%). Table 1 describes tumour location, radiologic appearance, histology and treatment.

3.2 Pathology data

Tumour samples were obtained from biopsy 5/25 (20%), resection 18/25 (72%) and autopsy 2/25 (8%). 2/25 (8%) biopsies were non-informative. Among the 23/42 cases with a histopathological diagnosis the majority of tumours (22/23) were found to be astrocytomas: 5 of these were pilocytic astrocytomas (WHO-grade I), 3 diffuse astrocytomas (WHO-grade II), 8 anaplastic astrocytomas (WHO-grade III) and 6 glioblastomas (WHO-grade IV). One tumour was diagnosed as atypical teratoid / rhabdoid tumour (WHO-grade IV). The WHO-grade of the tumour was high (grade III-IV) in 15/23 (65%) and low (grade I-II) in 8/23 (35%) patients (Table 1).

Table 1 Demographic and brainstem tumour characteristics of all 42 children.

Tumour location		
Mesencephalon	4	10%
Mesencephalon to pons	7	17%
Pons	10	24%
Pons to medulla oblongata	8	19%
Medulla oblongata	4	10%
Medulla oblongata to medulla spinalis	4	10%
whole brainstem	5	12%
Radiological appearance (n=34)		
Diffuse intrinsic	25	74%
Exophytic	4	12%
Focal intrinsic	3	9%
Cervicomedullary	2	6%
no imaging for review availabe	8	
Histopathological diagnosis (n=23)		
Pilocytic astrocytoma WHO I	5	22%
Diffuse astrocytoma WHO II	3	13%
Anaplastic astrocytoma WHO III	8	35%
Glioblastoma WHO IV	6	26%
Atypical teratoid / rhabdoid tumour WHO IV	1	4%
Non-informative	2	
Treatment received		
Partial or total resection	19	45%
Radiotherapy	15	36%
Chemotherapy	12	29%
Cerebrospinal fluid diversion	7	17%

3.3 Imaging data

Detailed MRI data was available from medical or radiology reports. Additionally, re-analysis of neuroimaging together with a neuro-radiologist was performed in 34/42 cases. This information is described in Table 2.

Table 2 Patient and tumour characteristics of 42 children with brainstem tumours.

Case No.	Age at Diagnosis (yrs), Sex	PSI (days)	Location	Classification based on re-evaluation of neuroimaging	Histology (incl. WHO Tumor Grade)	Management	Clinical Course	FU Time Since Diagnosis (yrs)
39	6.8, M	7	Pons	Diffuse intrinsic pontine glioma			PD	0.2
19	4.6, F	30	Pons	Diffuse intrinsic pontine glioma	Astrocytoma, anaplastic (WHO III)		DOD	0.2
8	9.2, M	55	Pons	Diffuse intrinsic pontine glioma			PD	0.2
35	8.4, F		Pons	Diffuse intrinsic pontine glioma	Astrocytoma, anaplastic (WHO III)		DOD	0.7
6	10.4, F	14	Pons	Diffuse intrinsic pontine glioma		R	DOD	0.6
24	9.8, F	23	Pons	Diffuse intrinsic pontine glioma		R C	DOD	1.4
12	5.1, M	210	Pons	Diffuse intrinsic pontine glioma		R Sh	SD	0.3
25	3.5; F	24	Pons	Diffuse intrinsic pontine glioma	Glioblastoma multiforme (WHO IV)	S	SD	0.1
33	6.4, F	39	Pons	Diffuse intrinsic pontine glioma	Glioblastoma multiforme (WHO IV)	S	DOD	0.8
11	6.2, F	150	Pons	Diffuse intrinsic pontine glioma	Astrocytoma, anaplastic (WHO III)	S	PD	0.1
40	6.4, F	150	Pons and Medulla oblongata	Diffuse intrinsic pontine glioma	Astrocytoma, anaplastic (WHO III)		DOD	0.4
10	12.2, F	47	Pons and Medulla oblongata	Diffuse intrinsic pontine glioma		R C	PD	0.5
9	13.1, M	45	Pons and Medulla oblongata	Diffuse intrinsic pontine glioma	Glioblastoma multiforme (WHO IV)	R C S	DOD	0.1
20	8.2, M	21	Pons and Medulla oblongata	Diffuse intrinsic pontine glioma	Glioblastoma multiforme (WHO IV)	R C S Sh	PD	1.0
41	2.3, F	28	Pons and Mesencephalon	Diffuse intrinsic pontine glioma		C	DOD	0.7
23	2.8, F	182	Pons and Mesencephalon	Diffuse intrinsic pontine glioma		C	DOD	3.0
34	1.5, F	1	Pons and Mesencephalon	Diffuse intrinsic pontine glioma			DOD	0.1
2	6.0, M	59	Pons and Mesencephalon	Diffuse intrinsic pontine glioma		R	DOD	1.4
5	5.9, M	140	Pons to Brachium pontis and Medulla oblongata	Diffuse intrinsic pontine glioma	Glioblastoma multiforme (WHO IV)	R S	PD	0.8
37	7.1, M	49	Pons to Mesencephalon and Cerebellum	Diffuse intrinsic pontine glioma	Astrocytoma, anaplastic (WHO III)	R S Sh	PD	0.3
31	5.2, M	67	Pons to Mesencephalon and Medulla oblongata	Diffuse intrinsic pontine glioma			DOD	0.6
27	14.3, M	150	Pons to Mesencephalon and Medulla oblongata	Diffuse intrinsic pontine glioma		Sh	PD	0.1
36	8.9, M	10	Pons to Mesencephalon and Medulla oblongata	Diffuse intrinsic pontine glioma		R C	DOD	1.2
30	4.7, F	25	Pons to Mesencephalon and Medulla oblongata	Diffuse intrinsic pontine glioma		R C	DOD	1.2
32	9.2, M	16	Pons to Mesencephalon and Pedunculus cerebelli	Diffuse intrinsic pontine glioma	Astrocytoma, anaplastic (WHO III)	S	PD	0.5
16	1.7, F	189	Medulla oblongata and Medulla spinalis	cervicomedullary	Astrocytoma, anaplastic (WHO III)	C	PD	6.0
29	1.0, M	7	Medulla oblongata and Medulla spinalis	cervicomedullary	Non-informative biopsy	S	SD	3.0
42	4.4, M	365	Medulla oblongata	exophytic dorsally	Astrocytoma, pilocytic (WHO I)	C S	SD	1.7
7	1.3, M	270	Medulla oblongata	exophytic dorsally	Astrocytoma, diffuse (WHO II)	R C S Sh	PD	21.9
18	5.1, F	395	Medulla oblongata and Medulla spinalis	exophytic dorsally	Astrocytoma, pilocytic (WHO I)	S	SD	0.6
15	2.4, M	180	Tectum mesencephali	exophytic dorsally	Glioblastoma multiforme (WHO IV)	R C S Sh	PD	3.2
3	12.4, M		Mesencephalon	focal	Astrocytoma, anaplastic pilozytic (WHO III)	R S	PD	0.6
13	14.6, F		Tectum mesencephali	focal	Astrocytoma, fibrillary (WHO II)	R S Sh	PD	1.8
14	9.3, M	365	Tectum mesencephali	focal	Astocytoma, fibrillary (WHO II)	S	SD	0.8
26	0.4, M	35	Medulla oblongata		Astrocytoma, pilocytic (WHO I)	S	DOD	0.3
22	3.8, F	180	Medulla oblongata			S	SD	0.1
28	1.7, M	6	Medullo oblongata and Medulla spinalis		Astrocytoma, pilocytic (WHO I)		DOD	0.3
4	5.6, F	180	Pons and Medulla oblongata		Astrocytoma, pilocytic (WHO I)	S	PD	14.8
38	3.8, F	42	Pons and Mesencephalon				PD	0.0
1	5.4, F		Pons to Medulla oblongata and Brachium pontis				SD	1.6
21	0.0, M	0	Pons to Mesecephalon, Medulla oblongata and Pedunculus cerebellaris		Atypical teratoid / rhabdoid tumour (WHO IV)		DOD	0.0
17	4.4, M	60	Pons, Medulla oblongata				SD	16.0

PSI = Pre-diagnostic Symptomatic Intervall; R = Radiotherapy; C = Chemotherapy; S = Surgery; Sh = Shunt; DOD = Death of Disease; SD = Stable Disease; PD = Progressive Disease; FU = follow-up

The pons was involved in 30/42 (71%), followed by the medulla, which was involved in 21/42 (50%), and the mesencephalon was involved in 16/42 (38%) patients. Tumours involved more than one brainstem region in 20/42 (48%) cases. Further data regarding patients and tumour characteristics are detailed in Table 2.

Regarding the 34 patients where review of neuroimaging was possible, the radiological tumour appearance was diffuse intrinsic in 25/34 (74%), exophytic in 4/34 (12%), focal intrinsic in 3/34 (9%) and cervicomedullary in 2/34 (6%) (Table 2).

3.4 Pre-diagnostic symptomatic interval

In 38/42 patients, medical records allowed to define a PSI (Table 2). In 29/38 (76%) patients, medical records allowed a subdivision of the PSI into parents' delay and doctor's delay. The median PSI was 48 days (range 0 to 395 days) with a median parents' delay of 19 days (range 0 to 365 days) and a median doctor's delay of 7 days (range 0 to 270 days).

3.5 Frequency of signs and symptoms at diagnosis

The initial signs and symptoms at the time of diagnosis are presented in Table 3. 41 different symptoms and signs were identified. Regarding one patient, signs and symptoms could not be retrieved from the medical record, so this patient was excluded from statistics below. None of the patients were monosymptomatic. All 41 patients had two (2/41 [5%]), three (4/41 [10%]), four (4/41 [10%]), five (5/41 [12%]), six (4/41 [10%]), and seven (3/41 [7%]) or more (18/41 [44%]) signs/symptoms. One patient was asymptomatic at time of diagnosis, and diagnosis was an incidental finding.

Signs and symptoms of increased intracranial pressure were observed in 25/41 (61%) patients at diagnosis. 13/41 (32%) had hydrocephalus. Cranial nerve palsies were the most frequent sign overall (25/41 [61%]), and they usually affected eye movement. The abducens nerve was widespread (15/41 [37%]), followed by the facial nerve (13/41 [32%]) and oculomotorius nerve (3/41 [7%]). Other frequent symptoms/signs at diagnosis were: abnormal gait and coordination (24/41 [59%]), squint and diplopia (24/41 [59%]), ataxia (19/41 [46%]), headache (16/41 [39%]), head tilt (15/41 [37%]), nausea and vomiting (14/41 [34%]), pyramidal signs (13/41 [32%]), hydrocephalus (13/41 [32%]), nystagmus (12/41 [29%]), behavioural change (9/41 [22%]) and hemiparesis (8/41 [20%]). In children younger than 4 years (12/41 [29%]), the most common initial symptoms and signs were abnormal gait and coordination (7/12 [58%]) and head tilt (7/12 [58%]).

Table 3 Frequency of signs and symptoms at diagnosis in children with brainstem tumours depending on age.

Signs and symptoms	*All (n=41)*		*Age < 4 years (n=12)*		*Age > 4 years (n=29)*	
Cranial nerve palsies (NOS)	25	61%	4	33%	21	72%
Symptoms of raised ICP (NOS)	25	61%	4	33%	21	72%
Squint and diplopia	24	59%	4	33%	20	69%
Abnormal gait and coordination	24	59%	7	58%	17	59%
Ataxia	19	46%	4	33%	15	52%
Headache	16	39%	0	0%	16	55%
Abducens palsy	15	37%	2	17%	13	45%
Head tilt	15	37%	7	58%	8	28%
Nausea and vomiting	14	34%	1	8%	13	45%
Pyramidal signs (NOS)	13	32%	1	8%	12	41%
Facial palsy	13	32%	2	17%	11	38%
Hydrocephalus	13	32%	4	33%	9	31%
Nystagmus	12	29%	3	25%	9	31%
Behavioral change	9	22%	2	17%	7	24%
Hemiparesis	8	20%	4	33%	4	14%
Fatigue and sleepiness	7	17%	0	0%	7	24%
Enlargement of the head	6	15%	4	33%	2	7%
Hypoglossus palsy	5	12%	0	0%	5	17%
Dizziness	5	12%	0	0%	5	17%
Dysarthria	4	10%	0	0%	4	14%
Oculomotorius palsy	3	7%	0	0%	3	10%
Dysphagia	3	7%	0	0%	3	10%
Uvular deviation / glossopharyngeus palsy	3	7%	0	0%	3	10%
Tremor	3	7%	1	8%	2	7%
Trigeminus palsy	2	5%	0	0%	2	7%
Dehydratation	2	5%	0	0%	2	7%
Apathy	2	5%	0	0%	2	7%
Weigt gain	2	5%	0	0%	2	7%
Seizure	2	5%	1	8%	1	3%
Involuntary salivation	2	5%	1	8%	1	3%
Growth failure	2	5%	1	8%	1	3%
Developement delay	2	5%	1	8%	1	3%
Sphincter disturbance	2	5%	1	8%	1	3%
Lethargy	1	2%	0	0%	1	3%
Weight loss	1	2%	0	0%	1	3%
Sucking weakness	1	2%	0	0%	1	3%
Nervus vagus palsy	1	2%	0	0%	1	3%
Accessorius palsy	1	2%	0	0%	1	3%
Sleep disturbance	1	2%	1	8%	0	0%
Head banging	1	2%	1	8%	0	0%
Paraparesis	1	2%	1	8%	0	0%

ICP=intracranial pressure. NOS=not otherwise specified

For one patient signs and symptoms could not be identified out of clinical records, and this patient was excluded.

3.6 Treatment data

Partial or total resection was performed in 19/42 (45%) patients. 15/42 patients (36%) underwent radiation therapy, and 12/42 patients (29%) received chemotherapy. 7/42 patients (17%) underwent cerebrospinal fluid diversion with ventriculoperitoneal shunt. In 13/42 (31%) patients, treatment was palliative only.

3.7 Progression-free and overall survival

The median follow-up time of all 42 patients was 7.6 months (range 0 - 22.2 years). Tumour progression occurred in 33/42 patients (79%) and death due to tumour progression was documented in 17/42 (40%). The median progression-free survival was 5.7 months (95% CI, 2.8 to 8.7) (Figure 1) and the median overall survival was 16.6 months (95% CI, 11.5 to 21.6) as determined by the Kaplan-Meier method (Figure 2).

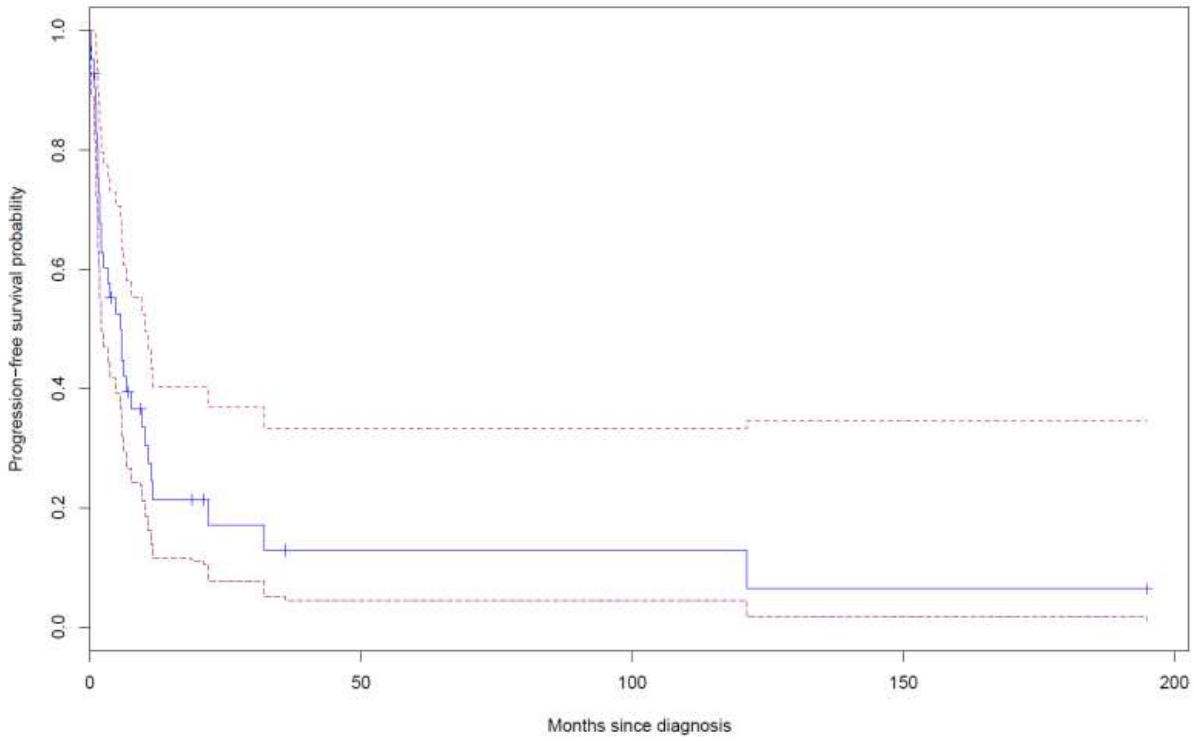

Figure 1. Progression-free survival with 95% confidence intervals for 42 children with brainstem tumours.

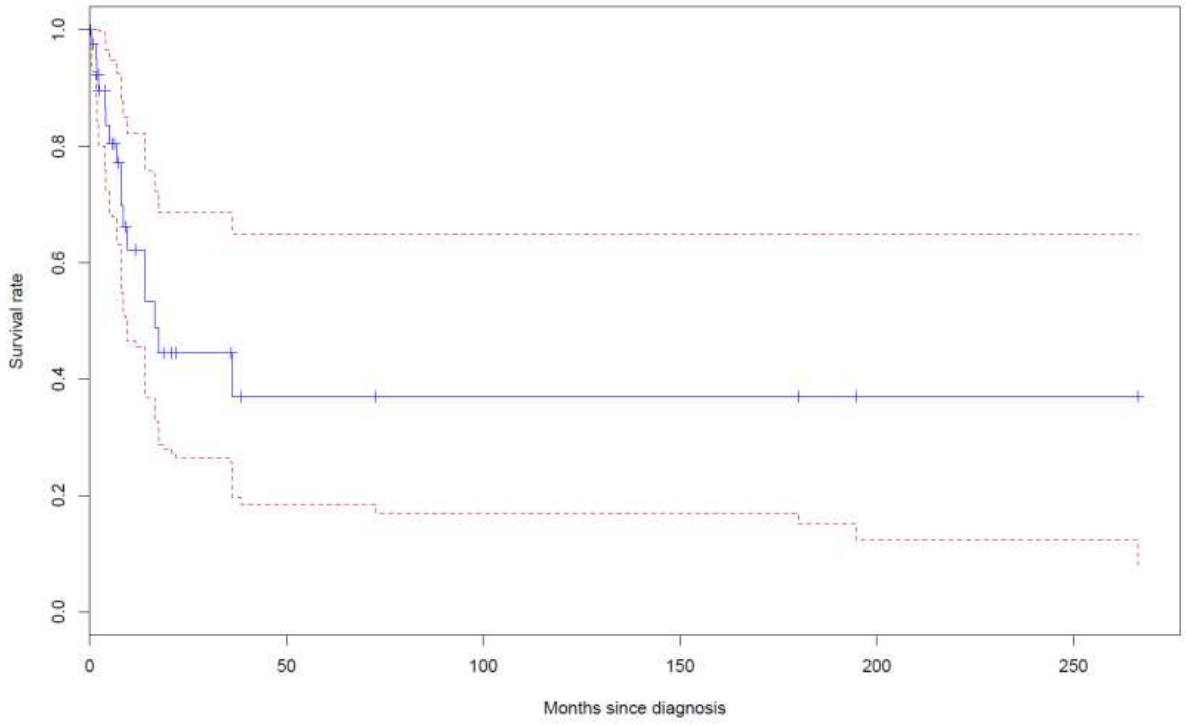

Figure 2. Overall survival with 95% confidence intervals for 42 children with brainstem tumours.

Patients with described tumour extension into pons, medulla and mesencephalon showed a tendency to worse overall survival (p=0.094) compared to children with tumours not affecting the entire brainstem. Median survivals of 14.1 months (95% CI, 2.7 to 25.6) and 36.3 months (95% CI, 3.7 to 68.9) were estimated for patients with tumour extensions to the entire brainstem, respectively for patients with tumours not affecting the entire brainstem.

Patients with tumour localization in the pons only, showed a median survival of 7.9 months (95% CI, 7.8 to 8.1) compared to the others with a median survival of 36.3 months (95% CI, 0 to 95.5) but the median survival was not significantly different (p=0.325). Patients with brainstem tumours not involving the pons did not show a significantly better overall survival rate than children with brainstem tumours with pontine involvement, but in general a better survival could be noticed (p=0.104).

Children with diffuse intrinsic brainstem gliomas showed a significant worse median progression-free survival of 4.8 months (95% CI, 0.5 to 9.1) compared to children with focal brainstem tumours (exophytic, focal intrinsic and cervicomedullary) with a median progression-free survival of 32 months (95% CI, 0 to 74.1) (p=0.001)(Figure 3).

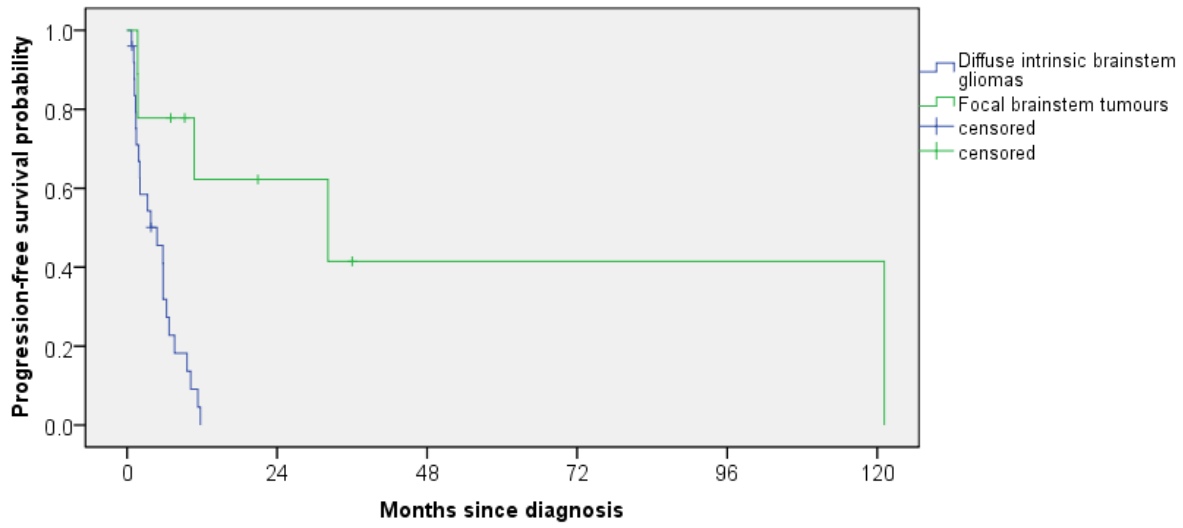

Figure 3. Progression-free survival probability of children with diffuse intrinsic brainstem gliomas compared to children with focal brainstem tumours.

Patients with diffuse intrinsic brainstem gliomas showed a median overall survival of 9.6 months (95% CI, 2.8 to 16.3). The median overall survival time of children with focal brainstem tumours (exophytic, focal intrinsic and cervicomedullary) could not be observed, and therefore the difference was statistically significant (p<0.001) (Figure 4).

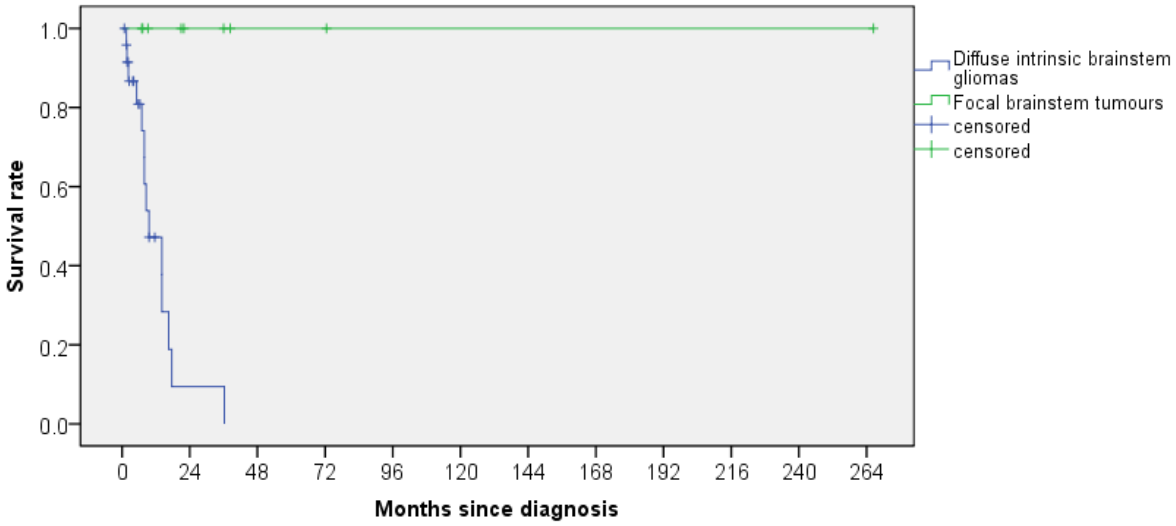

Figure 4. Overall survival of children with diffuse intrinsic brainstem gliomas compared to children with focal brainstem tumours.

Patients with diffuse intrinsic brainstem gliomas receiving surgery, radiotherapy, chemotherapy, or a combination of them, showed a median progression-free survival of 5.7 months (95% CI, 3.9 to 7.5) and a median overall survival of 14.2 months (95% CI, 8.4 to 20). Regarding patients with observational treatment, median progression-free survival was 1.5 months (95% CI, 0.5 to 2.5) and median overall survival was 5.2 months (95% CI, 0.7 to 9.7). The difference between progression-free survival (p=0.042) and overall survival (p=0.001) was significant (Figure 5 and Figure 6).

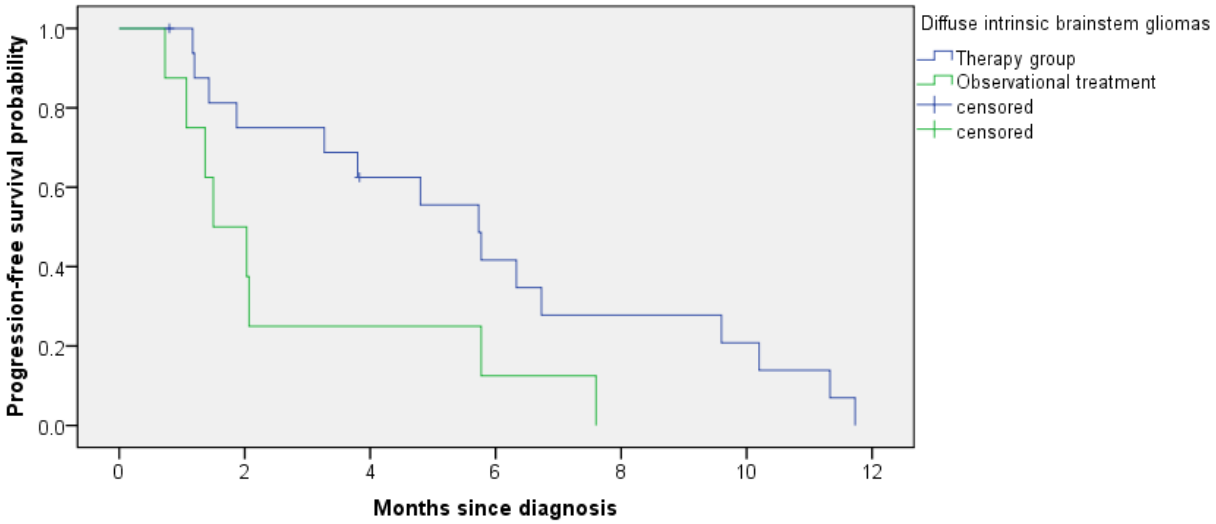

Figure 5. Progression-free survival of children with diffuse intrinsic brainstem gliomas receiving therapy compared to children with observational treatment.

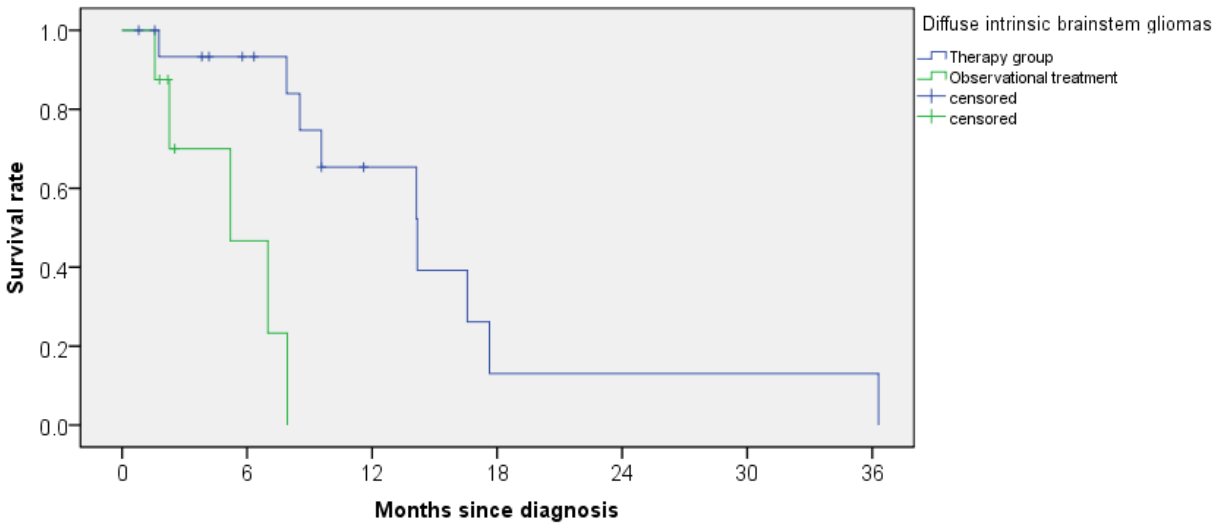

Figure 6. Overall survival of children with diffuse intrinsic brainstem gliomas receiving therapy compared to children with observational treatment.

4. Discussion

Paediatric brainstem tumours constitute a challenging group in terms of treatment. Although once considered to be a single entity, these tumours comprise several groups with heterogeneous biological behaviours [17]. Neuroimaging characteristics divide these tumours into two large groups: intrinsic tumours and focal tumours [6, 14]. The majority are intrinsic tumours diffusely infiltrating the pontine area and medulla oblongata [53]. Despite the attempts with radio- and chemotherapy, most cases have a fatal prognosis [26].

In our study population, there was no gender predominance, concurring with other studies [5, 7-13]. The median age at diagnosis of 5.5 years was found to be marginally lower compared with other studies [5, 8, 9, 12, 13]. There was one atypical teratoid / rhabdoid tumour in the brainstem diagnosed antenatal. Diffuse intrinsic brainstem tumours have also been reported in the neonate, with prognosis as poor as in older children [94]. But there are described spontaneous remissions of diffuse brainstem lesions in a neonate [95]. An increased frequency of brainstem tumours among children showing an underlying cancer predisposition (neurofibromatosis type 1) is already known and described [5, 79, 82, 83] and our found prevalence of about 5% has been as reported in the literature [5]. Both patients with NF 1 were alive at last follow-up, thus, as described in the literature, brainstem tumours in patients with NF 1 appear to have a much more favourable prognosis [79, 81-84].

As for tumour location within the brainstem, tumours most often involved the pons (71%) as also seen in other studies [5, 96]. The medulla was involved in 50% and the mesencephalon in 48%. Tumours involved more than one brainstem region in 20 cases (48%) which was clearly more than described in studies conducted in other areas [5]. The radiological tumour appearance of our analyzed patients was: 74% diffuse intrinsic, 12% exophytic, 9% focal intrinsic and 6% cervicomedullary. These radiological findings corresponded approximately with the relative frequency of different tumour types in the literature [6].

Children showed various signs and symptoms at diagnosis, usually already three or more symptoms. 41 different symptoms and signs were identified. More than half of the patients were already polysymptomatic at time of diagnosis. Signs and symptoms of increased intracranial pressure were noticed in 25/41 (61%). 25/41 (61%) presented with cranial nerve palsies also found as one of the most common deficits in other studies [96]. Abnormal gait and coordination was seen in 24/41 (59%), whereas others found abnormal gait and coordination to be by far the most common sign [97].

Children younger than 4 years were analyzed separately because they are known to present themselves differently than older children, not yet being able to clearly describe their symptoms. The most common initial sign was found to be abnormal gait and coordination (7/12 [58%]) and head tilt (7/12 [58%]).

The parents' delay with a median of 19 days was found to be longer than the doctor's delay with a median of 7 days. The median pre-diagnostic symptomatic interval was 48 days, and this duration of symptoms/signs was also found in other studies [8, 96]. The highly variable duration of symptoms prior to diagnosis seen in our patients is also described in the literature [96].

We found a tendency to better overall survival rate depending on anatomical tumour location within the brainstem. On the one hand, tumour extension into the whole brainstem showed a tendency to worse overall survival. In addition, median overall survival was 7.9 months in patients with tumour localization in the pons only compared to others with a median survival of 36.3 months, but due to the small patient sample this was not significant. In patients with brainstem tumours not involving the pons a direction towards better survival was observed. Brainstem tumours without pontine involvement have recently been described as being almost invariably low-grade tumours with excellent outcome, even with carful initial observation [5].

Median progression-free survival of 4.8 months and median overall survival of 9.6 months was noticed in children with diffuse intrinsic brainstem gliomas. Treatment of these patients with surgery, radiotherapy, chemotherapy or a combination thereof, resulted in a significantly better median progression-free ($p=0.042$) and median overall survival ($p=0.001$) than observational treatment.

Our study is based on a retrospective analysis of patients' records, which has clear limitations. Moreover, the number of patients is rather limited. On the other hand, the study has carefully taken into account data from children with brainstem tumours during a 30-year period at a single institution. Nevertheless, data may be confounded due to changes in diagnostic and treatment techniques that have taken place during the last three decades.

In summary, we demonstrated that survival for children with brainstem tumours remains poor to dismal. Children with brainstem tumours present with various often unspecific signs and symptoms. The combination of multiple neurological signs and symptoms should alert the clinician and lead to CNS imaging without delay.

New approaches to paediatric brainstem tumours are clearly needed.

5. References

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6. List of figures

7. List of tables